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The Effect of Erythrocyte-Containing Donor Blood Components in the Priming of the Cardiopulmonary Bypass Circuit on the Development of Systemic Inflammation During Correction of Congenital Heart Defects in Children

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Значение эритроцитсодержащих компонентов донорской крови в объеме первичного заполнения контура искусственного кровообращения в развитии системного воспаления при коррекции врожденных пороков сердца у детей

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Summary

Various pathological factors accompanying any cardiac surgery can cause intraoperative systemic inflammatory responses (SIR). As the number of cardiac surgical interventions grows worldwide, the issue of SIR prevention appears highly relevant.

Aim of the study. To determine the effect of not using donor blood components in the priming of the cardiopulmonary bypass circuit in children with septal congenital heart defects, operated under cardiopulmonary bypass, on the severity of SIR.

Material and methods. A prospective, randomized study included 40 children with a median age of 14 [12–22.5] months and weight of 8.8 [7.25–11] kg. All patients underwent radical correction of septal defect under cardiopulmonary bypass. The patients were divided into two groups depending on the use of donor blood components for priming the CPB. The severity of SIR was assessed using four specific serum biomarkers such as interleukin 1b (IL-1b), interleukin 6 (IL-6), interleukin 10 (IL-10), and tumor necrosis factor alpha (TNF-α), measured before the operation, after the CPB and 16 hours after the surgery. In addition, the intra- and postoperative periods were evaluated.

Results. The safety of the proposed strategy of skipping the donor blood was confirmed by lack of any organ dysfunction in all patients, as well as a significant difference in the balance of oxygen delivery and consumption. In addition, the levels of systemic inflammation markers after CPB were significantly higher in patients who had transfusion: IL-1b was 3.3 [3.2–3.48] pg/mL vs 2.86 [2.7–3.11] pg/mL (P=0.003) and TNF-α reached 1.81 [1.37–3.3] pg/mL vs 1.33 [1.26–1.76] pg/mL (P=0.034). Meanwhile, 16 hours post surgery, IL-6 and IL-10 levels were significantly higher in the group using donor blood components with IL-6 being 48.91 [33.89–57.6] pg/mL vs 31.56 [26.83–48.89] pg/mL (P=0.087) and IL-10 reaching 0.8 [0.76–1.43] pg/mL vs 0.69 [0.6–0.83] pg/mL (P=0.005).

Conclusion. The study demonstrates and confirms the safety and efficacy of cardiopulmonary bypass without using donor blood components to reduce the severity of the systemic inflammatory response in children undergoing correction of septal congenital heart defects.

Keywords: children; cardiac surgery; cardiopulmonary bypass; systemic inflammatory responses

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Any surgery is associated with factors such as anesthetics, changes in blood gas and acid-base balance, hemodynamic instability and many others, which can initiate systemic inflammatory responses (SIR) [1]. All these factors can be seen in pediatric congenital heart defects surgery characterized by large volume, invasiveness, and tissue damage as well as the use of cardiopulmonary bypass (CPB). The latter is associated with such abnormal factors as blood contact with the surface of the CPB circuit and the ambient air in the cardiotomy reservoir, hemodilution, exposure of blood cells to roller pumps, and non-pulsatile blood flow [2–4]. All these and other factors can trigger the first phase of SIR that initiates both humoral (complement system, coagulation system, cytokine release) and cellular (activation of white blood cells and platelets) reactions. Then the second phase ensues due to ischemia-reperfusion caused by aortic constriction and non-physiological nature of blood flow during CPB [2]. Besides, children, especially in their first year of life and weighing less than 10 kg, are highly susceptible to SIR development due to physiological characteristics [5, 6]. Multiple underlying mechanisms and causes of SIR warrant employment of various approaches to SIR control including intraoperative administration of steroids [7]. However, several studies demonstrated lack of effect of steroids on the risk of SIR even at high doses as pulse therapy [8, 9]. Increased hopes were pinned on hypothermia, but even its deep level, up to 24°C, during CPB in children also failed to reduce the risk of CHD [10]. Several interesting studies have shown a decrease in the level of inflammatory mediators during CPB in hypothermia group, however, no difference was found between the groups immediately after the main stage of surgery, indicating a delay release, rather than reduction in the total level of mediators [11]. In pediatric cardiac surgery, both standard and modified ultrafiltrations have proven to be effective in significant reducing the SIR intensity [12]. The similar effect was observed when using the WBC filters during CPB [13].

Another way of controlling CPB during cardiac surgery could be restricting transfusion of donor blood components. A mismatch between extracorporeal circuit volume and circulating blood volume of the child, especially in the first year of life, which can lead to critical hemodilution, is characteristic of surgeries using CPB. To prevent this complication, donor blood components (most commonly, red blood cell mass) are used for priming the CPB. However, several studies have demonstrated that transfusion itself can trigger SIR [14]. Currently, there is no common strategy on the use or avoidance of transfusion in children, especially those weighing 7 to 10 kg. Therefore, the issue of so-called «bloodless perfusion» in children is relevant both in terms of safety and effectiveness for the reduction of intraoperative SIR.

Material and Methods

The study was performed at the Department of Anesthesiology and Critical Care of the Research Institute for Complex Issues of Cardiovascular Diseases (RICID), Kemerovo, Russia. Forty children aged 6 to 36 months, mean age 14 [12–22.5] months, weight 8.8 [7.5–11] kg, who underwent planned radical correction of interventricular or interatrial septal defect under CPB, were examined. Power analysis was performed according to the formula $\mathbf{n=(t2*P*Q)/\triangle 2}$, where t is the critical value of Student test at the appropriate significance level (0.05); $\triangle$ is the marginal error (%); p is the proportion of cases in which the studied parameter was found (%); Q is the proportion of cases where the studied parameter was not found (100-P). According to this calculation, 196 patients were to be included in the study. However, since the effect of limiting red blood cell transfusion in reducing the severity of SIR was significant, a smaller sample of patients participating in the study was sufficient to prove that this effect was not random. This study was a pilot and at least 200 patients will be included in the future ones to be published. This was a prospective, randomized study approved by the local ethical committee of the RICID.

Using the envelope method, the patients were randomized into one of two following groups:

- Main group (CPB priming solution based on colloid/crystalloid solutions without red blood cell mass, 20 patients);
- Control group (CPB priming solution based on colloid/crystalloid solutions with red blood cell mass, 20 patients)

The patient characteristics are shown in Table 1.

All patients received anesthesiological support according to the same local regimen. After the patient was moved to the operating room, peripheral vein catheterization was performed under local anesthesia. Anesthesia was induced by administering propofol 2–3 mg/kg and fentanyl 5 mcg/kg. Pipecuronium bromide 0.1 mg/kg was used for muscle relaxation. Then tracheal intubation, central vein, radial artery and bladder catheterization were performed. At the beginning of the surgery, bolus injection of fentanyl 5 μg/kg was done. Maintenance anesthesia included continuous infusion of propofol 2–4 mg/kg/hr and fentanyl 5 μg/kg/hr using infusomate, and sevoflurane inhalation at 1.0–1.5 MAC.

Mechanical ventilation was performed using Datex-Ohmeda Avans (General Electric) semi-closed circuit (SIMV mode) under standard parameters in-

Table 1. Patient characteristics.

Characteristic	Values in groups		*P*
	Main	Control	
Number of patients	20 (50%)	20 (50%)	1
Male	7 (35%)	9 (45%)	0.52
Female	13 (65%)	11 (55%)	0.52
Age (months)	15 [12–23.3]	13 [11–21.3]	0.27
Height (cm)	81 [76–86]	75 [71.3–84.3]	0.14
Body weight (kg)	10.5 [9.2–11.3]	9.2 [8.7–11.8]	0.15
Laboratory blood parameters before surgery			
WBC count, $\times 10^9$/l)	7.4 [6.6–7.9]	7.5 [7–9]	0.17
RBC count, $\times 1^{012}$/l)	4.6 [4.5–4.75]	4.6 [3.9–5]	0.7
Hemoglobin, g/L	118.5 [115–121.3]	117 [112.8–119]	0.29
Hematocrit, %	36 [34–38]	35 [33–37]	0.34
Direct bilirubin, μmol/l	2.4 [2.1–3.3]	2.9 [2.1–3.7]	0.54
Indirect bilirubin, μmol/l	4.3 [2.5–5.5]	4.5 [2.4–6.7]	0.68
Creatinine, μmol/l	38.5 [30.5–44.3]	31 [24.3–43.3]	0.23
Urea, mmol/l	3.8 [3.4–4.3]	4 [3–5]	0.98
Preoperative NGAL, ng/ml	49.19 [24.3–100.1]	45.98 [34.58–98.98]	0.3
Surgery			
Diagnosis			
ASD	15 (75%)	15 (75%)	1
VSD	5 (25%)	5 (25%)	1
Surgical approach			
Median sternotomy	14 (70%)	15 (75%)	0.85
Lateral sternotomy	6 (30%)	5 (25%)	0.85
Duration of surgery	196 [188–203]	189 [181–200]	0.3
CPB duration (min.)	40.5 [33–47]	45 [35–49.5]	0.5
Duration of aortic clamping (min.)	27.5 [20.3–33]	29 [22.3 –36.3]	0.59

Note. Differences were considered significant at $P<0.05$. ASD — atrial septal defect; VSD — ventricular septal defect; CPB — cardiopulmonary bypass; WBC — white blood cells; RBC — red blood cells; NGAL — neutrophil gelatinase-associated lipocalin

cluding FiO_2 = 0.25–0.3, Vt = 6–8 ml/kg; Pi = 10–15 cm H_2O; PEER = 5–8 cm H_2O; Ti:Te = 1:2. CO_2 in exhaled air was monitored.

The CPB was performed according to the standard local procedure. The Maquet HL 20 device was used. The Terumo Baby Fx-05 and Sorin Dideco D101 membrane oxygenators werre used. Priming volume was 300 ml for both types of oxygenators. The choice of oxygenator depended on the estimated perfusion volume rate on CPB machine. All patients received 15% mannitol 500 mg/kg, 5% sodium bicarbonate 1.5 ml/kg, and heparin 6 units for each ml of the priming solution. The colloid fluid was 10% albumin 1 g/kg body weight (added only to the CPD machine). The crystalloid fluid was sterofundin, which volume was calculated as the difference between the total volume of priming solution and the rest of the components. Erythrocyte suspension 10 ml/kg with the removed WBC and platelets layer and storage time not exceeding 5 days was added. All patients received heparin 300 IU/kg with mandatory follow-up AST measurement prior to CPB. The composition of the priming volume in the groups is shown in Table 2.

The CPB was performed with perfusion index of 3.0 L/min/m2 in normothermic mode (nasopharyngeal probe temperature 37°C, without using pulsatile mode). Gas mixture flow into oxygenator was approximately 2 times less than the perfusion volume rate. Oxygen fraction in the gas mixture was regulated according to acid base balance data and ranged between 40 and 60%. Blood CO_2 tension was monitored using arterial blood analysis and controlled using the tidal volume of the gas mixture.

For cardioplegia, the cold Custodiol solution 50 ml/kg was used with exposure of at least 8 minutes. Cardioplegic solution was delivered in the antegrade direction into the aortic root. Special kits with Medtronic heat exchanger were used to deliver the solution. The waste cardioplegic solution was aspirated into the cardiotomy tank of oxygenator. Excessive hemodilution during cardioplegia and after it was avoided since during the whole CPB ultrafiltration aimed at elimination of excessive fluid perfusate was being performed. The Maquet BC 20 plus ultrafiltration column was used. Blood sampling for the column was performed from the arterial line, after its exit from the oxygenator for Terumo Baby Fx-05 and after the arterial filter for Sorin Dideco D101. Blood from the column was returned to the venous line at the connection point with the cardiotomy reservoir. Necessary rarefaction for ultrafiltration was created by vacuum pump connected to the column.

After completion of CPB, all patients underwent modified ultrafiltration with the same connection scheme for blood collection as in conventional ultrafiltration described above, but with return of concentrated blood into the cannula of inferior vena cava.

Table 2. The priming composition of CPB circuit in the groups.

Priming component, ml	Mean volume in groups, ml		*P*
	Main	Control	
Sterofundin	199.1 [192.2–212.8]	166,8 [154.2–174.9]	0.08
Mannitol, 15%	34.,0 [29.4–36.3]	29,7 [27.9–32.5]	0.05
Sodium bicarbonate, 5%	15.5 [13.7–16.5]	13,5 [13.0–14.8]	0.06
Albumin, 10%	51.5 [44.5–55.0]	—	—
RBC suspension	—	90 [84.5 – 98.5]	—

After completion of modified ultrafiltration, the vacuum ultrafiltration of perfusate remaining in cardiotome according to our original novel medical technique was done. After that, concentrated blood from ultrafiltration column was reinfused. This technique is necessary for maximum preservation of the patient's blood and allowed to maintain hemoglobin and hematocrit without transfusion.

The study used several specific markers such as interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 10 (IL-10) and tumor necrosis factor alpha (TNF-α), whose concentration in blood serum, according to literature data, can objectively assess the intensity of SIR [1, 15].

Blood test for measurement of the above-mentioned markers was performed at three time points points. FThe first, when the patient was admitted to the operating room, after the main vein catheterization, before the surgery. The second, immediately after CPB. The third, 16–18 hours after the surgery. Blood sampling was performed from the central venous catheter in the internal jugular vein.

In the perioperative period several laboratory and instrumental parameters were monitored during surgery and 16–18 hours after it. The results obtained at three time points are presented in the tables. The «before surgery» values were recorded after the central venous catheter placement, the «during CPB» values were registered 15 minutes after CPB initiation, and the «end of surgery» values were observed after the skin suturing.

Compliance between tissue oxygen delivery and consumption was assessed using venous blood saturation, blood lactate measurement and cerebral oximetry (rSO_2), the pulse oximetry (SpO_2) data were also evaluated. Renal function was monitored using urea and creatinine levels on day 1 post surgery and the neutrophil gelatinase-associated lipocalin (NGAL) level (marker of renal damage) [16]. Liver function was monitored using the direct and indirect bilirubin levels. The early postoperative period was evaluated, in addition to all of the above, by measurement of drainage losses, duration of ventilation and ICU stay, frequency of use and dosage of inotropic drugs. Epinephrine 0.05 μg/kg/min was used as the inotropic agent. The groups did not differ significantly in the duration of hemodynamic support. Polyionic solution (Sterofundin) and 5% glucose (1:1) were used for intravenous fluid therapy. The volume of intravenous fluid and urine output were assessed during 16 hours after the surgery.

Statistical analysis was done using the BioStat Pro 5.9.8 software. The nonparametric statistics was mostly employed due to non-normal distribution of variables as determined by Shapiro–Wilk criterion at $P<0.05$. Data were presented as median (*Me*), upper (*Q1*), and lower quartiles (*Q3*). Comparative analysis of quantitative variables was performed using Mann–Whitney test [17]; Wilcoxon criterion was used for paired variables. Comparative analysis of qualitative variables was performed using a 2×2 contingency table and Chi-square test for absolute values. Differences were considered significant at $P<0.05$.

Results and Discussion

The intraoperative values in both groups are compared in Table 3. Hemoglobin and hematocrit values were significantly higher during and after CPB in the control group patients received the RBC mass. However, despite the risk of hemic hypoxia in the main group, oxygen delivery and consumption values were within the reference range. Venous blood saturation did not differ between the groups during the CPB, but was different at the end of surgery (71% [69.8–73] vs 73% [71.8–77], $P=0.01$), with higher values in the control group. Meanwhile, the blood lactate level did not differ between the groups at both time points. Monitoring of oxygen status showed that values of pulse oximetry at all time points also did not significantly differ. When assessing the risk of cerebral perfusion disorders, we found that the intergroup difference according to NIRS monitoring results was seen only at the end of the surgery. Current research in this area emphasizes the importance of the change in the NIRS monitoring parameters versus baseline rather than their absolute values. Thus, a decrease by 20% [18], and according to some data, even by 10% [19] of NIRS values vs the baseline appears to be dangerous, which was not observed among the studied patients.

The postoperative parameters are characterized in Table 4. Hemoglobin and hematocrit levels did not change compared with the intraoperative period, being significantly higher in the transfusion group, as well as the red blood cell count. Similarly, venous blood saturation was higher in the controls than in the main group: 76.5% [73 to 80] vs 70% [68.8 to 73.3], respectively ($P=0.001$), with no difference in blood lactate level. In addition, the groups differed in blood leukocyte counts, $8.5*10^9$ [7.9–11.1] and

Table 3. Intraoperative parameters in the studied groups.

Parameter	Values in groups		*P*
	Main	Control	
Laboratory			
Hemoglobin during CPB, g/l	87 [81.0–91.3]	92 [87.3–97.3]	0.008
Hematocrit during CPB, %	25,5 [24.0–27.0]	29 [27.8–31.0]	<0.001
Hemoglobin at the end of surgery, g/l	106.0 [101.8–110.3]	130.5 [104.0–125.5]	<0.001
Hematocrit at the end of surgery, %	31.5 [30–33.3]	40.0 [38.8–41.5]	<0.001
Venous blood oxygen saturation during CPB, %	85.0 [83.8–89.0]	88.5 [86,0–90.0]	0.26
Venous blood oxygen saturation at the end of surgery, %	71.0 [69.8–73.0]	73.0 [71.8–77.0]	0.01
Blood lactate during CPB, mmol/l	1.5 [1.3–1.8]	1.5 [1.2–1.9]	0.87
Blood lactate at the end of surgery, mmol/l	1.5 [1.3–1.7]	1.5 [1.2–1.7]	0.46
Preoperative NGAL, ng/ml	49.2 [24.3–100.1]	46.0 [34.6–99.0]	0.3
Monitoring			
Preoperative SpO_2, %	97.0 [90.5–98.0]	98.0 [95.5–98.5]	0.33
SpO_2 at the end of surgery, %	99.0 [98.0–99.0]	99.0 [99.0–100.0]	0.03
Preoperative rSO_2, %	65.0 [61.5–73.5]	67.0 [61.5–70.5]	0.77
rSO_2 during CPB, %	83.0 [80.5–86.5]	85.0 [81.5–87.0]	0.40
rSO_2 at the end of surgery, %	70.5 [69.8–75.0]	77.0 [74.5–78.0]	0.008
Inotropic drug use			
Number of patients on inotropic drugs	4 (20%)	5 (25%)	0.7
Water balance			
Intravenous infusion volume, ml/kg	15.6 [13.5–16.4]	15.7 [12.8–17.4]	0.31
Urine output, ml/kg	11.0 [9.0–12.4]	10.5 [9.3–12.3]	0.43
Ultrafiltration volume during CPB, ml/kg	11.0 [10.1–13.3]	11.7 [10.2–13.5]	0.37

Note. The volume of intravenous fluid and urine output were monitored during the intraoperative period. For intravenous infusion, a polyionic solution (Sterofundin) was used. SpO_2 — blood oxygen saturation; rSO_2 – regional tissue oxygen saturation. Differences were considered significant at $P<0.05$.

Table 4. Postoperative parameters in the studied groups.

Parameter	Values in groups		*P*
	Main	Control	
Laboratory parameters			
Hemoglobin, g/l	101.0 [98.8–107.0]	124.0 [113.0–127.0]	<0.001
Hematocrit, %	30.0 [29.0–32.0]	34.0 [33.0–36.0]	<0.001
Oxygen saturation in venous blood, %	70.0 [68.8–73.3]	76.5 [73.0–80.0]	<0.001
Blood lactate, mmol/l	1.2 [1.1–1.35]	1.2 [1.08–1.3]	0.67
RBC count, $\times 10^{12}$/l	3.8 [3.6–4.1]	4.8 [4.5–5.0]	<0.001
WBC count, $\times 10^{9}$/l	8.5 [7.9–11.1]	10.8 [9.3–12.8]	0.013
Direct bilirubin, μmol/l	2.9 [2.2–3.2]	3.3 [2.3–4.4]	0.29
Indirect bilirubin, μmol/l	3.8 [2.7–4.9]	9.5 [4.9–13.0]	<0.001
Creatinine, μmol/l	26.5 [19.8–31.0]	32.5 [26.0–40.0]	0.015
Urea, mmol/l	3.7 [3.1–4.9]	4.5 [4.0–5.5]	0.032
Postoperative NGAL, ng/ml	87.3 [41.3–159.1]	74.5 [49.5–136.2]	0.46
Monitored parameters			
Drainage loss on Day 1 after surgery, ml/kg	54.6 [46.4–84.0]	68.0 [53.3–82.4]	0.3
Duration of stay in the ICU, hours	23.5 [21.0–29.0]	23.0 [21.8–41.5]	0.97
Duration of mechanical ventilation, hours	7.0 [6.0–8.0]	8.0 [6.8–9.0]	0.34
Inotropic drugs			
Number of patients on inotropic drugs	4 (20 %)	5 (25 %)	0.7
Water balance			
The volume of fluid infusions during ICU stay, ml	64.0 [6270–69.2]	61.0 [59.4–64.9]	0.1
Urine output during ICU stay, ml	24.0 [22.0–26.5]	28.0 [22.5–30.0]	0.08

Note. The table shows parameters recorded on the day following the surgery. The duration of mechanical ventilation was defined as the time from the moment of intubation to the moment of extubation and initiation of spontaneous breathing. The volume of fluid infusions included intravenous + enteral fluid intake. Differences were considered significant at $P<0.05$.

$10.8*10^9$ [9.3–12.8] (P=0.013), with higher values among patients who received red blood cell mass intraoperatively. Direct bilirubin concentrations did not differ between the groups, and indirect bilirubin levels were higher in the controls being 9.5 μmol/L [4.9–13] vs 3.8 μmol/L [2.7–4.9] (P=0.013). Although bilirubin level was within the reference range in both groups, significant increase of indirect bilirubin the control group was probably due to hemolysis of donor erythrocytes [20], rather than any liver damage. Postoperative blood creatinine levels were 26.5 μmol/L [19.8–31] in the main group and 32.5 μmol/L [26–40] in the control group (P=0.015). Blood urea level was 3.7 mmol/L [3.1–4.9] in the main group vs 4.5 mmol/L [4– 5.5] in the controls (P=0.032). The NGAL concentration did not differ

Table 5. Changes in SIR markers.

Parameter	Values in groups		*P*
	Main	Control	
IL-1b BS, pg/ml	2.6 [2.2–2.8]	2.6 [2.5–3.0]	0.16
IL-1b ES, pg/ml	2.9 [2.7–3.1]	3.3 [3.2–3.5]	0.003
IL-1b 16 hours after surgery, pg/ml	2.7 [2.6–3.1]	2.8 [2.7–3.1]	0.46
IL-6 BS, pg/ml	2.5 [2.4–2.7]	2.6 [2.4–5.9]	0.21
IL-6 ES, pg/ml	29.1 [15.5–40.6]	27.6 [16.9–48.5]	0.18
IL-6 16 hours after surgery, pg/ml	31.6 [26.8–48.9]	48.9 [33.9–57.6]	0.087
IL-10 BS, pg/ml	0.6 [0.6–0.7]	0.6 [0.6–0.9]	0.39
IL-10 ES, pg/ml	7.9 [4.5–12.1]	8.8 [5.6–38.5]	0.07
IL-10 16 hours after surgery, pg/ml	0.7 [0.6–0.8]	0.8 [0.8–1.4]	0.005
TNF-α BS, pg/ml	1.3 [1.1–1.5]	1.2 [1.2–1.3]	0.19
TNF-α ES, pg/ml	1.3 [1.3–1.8]	1.81 [1.4–3.3]	0.034
TNF-α 16 hours after surgery, pg/ml	1.2 [1.1–1.6]	1.3 [1.2–1.9]	0.1

Note. BS — before surgery; ES — end of surgery. Differences were considered significant at $P<0.05$.

between the groups before surgery (49.19 ng/mL [24.3–100.1] vs 45.98 ng/mL [34.58–98.98] for the main and control groups, respectively) and 16 hours after surgery (87.3 ng/mL [41.3–159.02] vs 74.5 ng/mL [49.46–136.15], respectively). The increase in NGAL level on the next day after surgery was significant for both main (P=0.036) and control (p=0.039) groups. There were no differences between the groups in the volume of drainage loss, duration of mechanical ventilation and ICU stay, as well as the frequency of inotropic drugs administration.

The IL-1 level peaked at the 2nd time point (after completion of CPB) (2.86 ng/mL in the main group and 3.3 ng/mL in the control group) for both groups, and was significantly higher ($P<0.001$) than the baseline values (2.57 ng/mL in the main group and 2.58 ng/mL in the control group). Sixteen hours after surgery, the concentration of this marker decreased while remaining significantly higher than the baseline values (2.72 ng/mL in the main group and 2.82 ng/mL in the control group) ($P<0.001$). Intergroup comparison revealed a significant difference only at 2nd time point (P=0.003) with a higher IL-1 concentration in the group which underwent transfusion.

The peak IL-6 concentration, unlike the previous marker, was found at the 3rd time point for both groups. Blood levels of IL-6 were significantly higher in the main and control groups compared with baseline values (2.47 ng/mL and 2.64 ng/mL, respectively), both after completion of CPB (29.1 ng/mL in the main group and 27.58 ng/mL in the controls) and the morning after surgery (31.56 ng/mL in the main group and 48.91 ng/mL in the controls) ($P<0.001$). There was a trend towards differences in this parameter between the groups at 3rd time point (P=0.087).

The level of IL-10 significantly increased vs baseline values (0.62 ng/mL in both main and control groups) after completion of CPB (7.92 ng/mL in the main group and 8.78 ng/mL in the control group, $P<0.001$). However, on the following day in the main group no significant difference from the baseline value was observed (0.69 ng/ml, P=0.49), unlike the control group, where the value was significantly higher (0.8 ng/ml, P=0.006). An intergroup difference was revealed 16 hours post surgery: IL-10 level was significantly higher in the control group (P=0.005). After CPB completion, only a trend to an increase in this parameter was found (P=0.07).

The levels of TNF-α did not differ between patient groups at the first measurement (1.29 ng/mL in the main group and 1.21 ng/mL in the controls, P=0.19). Maximum concentration of the cytokine was recorded at the second timepoint in both groups (1.33 ng/ml in the main group and 1.81 ng/ml in the control group). Main group values, however, did not differ significantly versus baseline (P=0.21), unlike the control values (P=0.006). At timepoint 3, TNF-α values in the main group did not differ from baseline. TNF-α concentration after CPB completion was significantly higher in the group using red blood cell mass than in the main group (P=0.034).

From the perspective of SIR development, it is important that the WBC count (an indicator of inflammation) was significantly higher in the transfusion group during early postoperative days (Table 5). When analyzing the changes in specific SIR markers, such a difference becomes evident: 3 of the 4 markers studied (IL-1, IL-10 and TNF-α) had higher levels in the group receiving red blood cell mass immediately after the completion of CPB. This relationship with transfusion has its own explanation: any component of donor blood is a foreign agent for the patient's immune system and the activation of the inflammatory response is quite natural, as shown in many recent studies [21–23].

The study did not find any other negative sequelae of transfusion, except for higher SIR. Other publications, however, discuss the risk factors of transfusions that include increased mortality due to infections, lung damage [24, 25] and even postoperative delirium [26, 27]. Our study posits that the development of techniques to reduce the perioperative use of donor blood components is prom-

ising that corraborates current trends in cardiac anesthesiology [28].

Conclusion

There is strong evidence of safety and effectiveness of cardiopulmonary bypass without the use of donor blood components to reduce the severity of the systemic inflammatory response in children during correction of septal congenital heart disease.

References

1. *Botwinski C.A.* Systemic inflammatory response syndrome. *Neonatal Network*. 2001; 20 (5): 21–28. DOI: 110.1891/0730-0832.20.5.21. PMID: 12144219.
2. *Warren O.J, Smith A.J, Alexiou C., Rogers P.L.B, Jawad N., Vincent C., Darzi A.W., Athanasiou T.* The inflammatory response to cardiopulmonary bypass: part 1-mechanisms of pathogenesis. *Journal of Cardiothoracic and Vascular Anesthesia*. 2009; 23: 223–231. DOI: 10.1053/ j.jvca.2008.08.007. PMID: 18930659.
3. *Wang Y., Lin X., Yue H., Kissoon N., Sun B.* Evaluation of systemic inflammatory response syndrome-negative sepsis from a Chinese regional pediatric network. *Collaborative Study Group for Pediatric Sepsis in Huai'an BMC Pediatric*. 2019; 8; 19 (1): 11. DOI: 10.1186/ s12887-018-1364-8.
4. *Toomasian C.J., Aiello S.R., Drumright B.L., Major T.C., Bartlett R.H., Toomasian J.M.* The effect of air exposure on leucocyte and cytokine activation in an in-vitro model of cardiotomy suction. *Perfusion* 2018; 33 (7): 538–545. DOI: 10.1177/0267659118766157. PMID: 29638199.
5. *Guvener M., Korun O., Demirturk O.S.* Risk factors for systemic inflammatory response after congenital cardiac surgery. *J Card Surg*. 2015; 30 (1): 92–96. DOI: 10.1111/jocs.12465. PMID: 25382731.
6. *Boettcher W., Merkle F., Huebler M., Koster A., Schulz F., Kopitz M., Kuppe H., Lange P., Hetzer R.* Transfusion-free cardiopulmonary bypass in Jehovah's Witness patients weighing less than 5 kg. *J Extra Corpor Technol*. 2005; 37 (3): 282–285. PMID: 16350381.
7. *Fudulu D.P., Gibbison B., Upton T., Stoica S.C., Caputo M., Lightman S., Angelini G.D.* Corticosteroids in pediatric heart surgery: myth or reality. *Front Pediatr*. 2018; 6: 112. DOI: 10.3389/fped.2018.00112. PMID: 29732365.
8. *Keski-Nisula J., Pesonen E., Olkkola K.T., Ahlroth T., Puntila J., Andersson S., Neuvonen P.J., Suominen P.K.* High-dose methylprednisolone has no benefit over moderate dose for the correction of tetralogy of Fallot. *Ann Thorac Surg*. 2016; 102 (3): 870–876. DOI: 10.1016/j.athoracsur.2016.02.089. PMID: 27154159.
9. *Dreher M., Glatz A.C., Kennedy A., Rosenthal T., Gaynor J.W.* A single-center analysis of methylprednisolone use during pediatric cardiopulmonary bypass. *J Extra Corpor Technol*. 2015; 47 (3): 155–159. PMID: 26543249.
10. *Xiong Y., Sun Y., Ji B., Liu J., Wang G., Zheng Z.* Systematic review and meta-analysis of benefits and risks between normothermia and hypothermia during cardiopulmonary bypass in pediatric cardiac surgery. *Paediatr Anaesth*. 2015; 25 (2): 135–142. DOI: 10.1111/pan. 12560. PMID: 25331483.
11. *Stocker C.F, Shekerdemian L.S., Horton S.B., Lee K.J., Eyres R., D'Udekem Y., Brizard C.P.* The influence of bypass temperature on the systemic inflammatory response and organ injury after pediatric open surgery: a randomized trial. *J. Thorac Cardiovasc Surg*. 2011; 142 (1): 174–180. DOI: 10.1016/j.jtcvs.2011.01.059. PMID: 21420106.
12. *Bierer J., Stanzel R., Henderson M., Sett S., Horne D.* Ultrafiltration in pediatric cardiac surgery review. *World J Pediatr Congenit Heart Surg*. 2019; 10 (6): 778–788. DOI: 10.1177/2150135119870176. PMID: 31701831.
13. *Alexiou C., Tang A.A.T., Sheppard S.V., Smith D.C., Gibbs R., Livesey S.A., Monro J.L., Haw M.P.* The effect of leucodepletion on leucocyte activation, pulmonary inflammation and respiratory index in surgery for coronary revascularisation: a prospective randomised study. *Eur J Cardiothorac Surg*. 2004; 26: 294–300. DOI: 10.1016/j.ejcts. 2004.04.017. PMID: 15296886.
14. *Delaney M., Stark P.C., Suh M., Triulzi D.J., Hess J.R., Steiner M.E., Stowell C.P., Sloan S.R.* Massive transfusion in cardiac surgery: the impact of blood component ratios on clinical outcomes and survival. *Anesth Analg*. 2017; 124 (6): 1777–1782. DOI: 10.1213/ANE. 0000000000001926. PMID: 28333704.
15. *Smok B., Domagalski K., Pawłowska M.* Diagnostic and prognostic value of IL-6 and sTREM-1 in SIRS and sepsis in children. *Mediators Inflamm*. 2020; 2020: 8201585. DOI: 10.1155/2020/8201585. PMID: 32655314.
16. *Staples A., LeBlond R., Watkins S., Wong C., Brandt J.* Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. *Pediatr Nephrol*. 2010; 25: 2321–2326. DOI: 10.1007/ s00467-010-1598-7. PMID: 20652327.
17. *Трухачева Н. В.* Математическая статистика в медико-биологических исследованиях с применением пакета Statistica. М.*ГЭОТАР-Медиа*. 2013: 379; ISBN 978-5-9704-2567-1. [*Trukhacheva N.V.* Mathematical statistics in biomedical research using the Statistica package. M. GEOTAR-Media. (in Russ.). 2013: 379. ISBN 978-5-9704-2567-1].
18. *Clark R.K., Lee E.V, Fish C.J., White R.F., Price W.J., Jonak Z.L., Feuerstein G.Z., Barone F.C.* Development of tissue damage, inflammation and resolution following stroke: an immunohistochemical and quantitative planimetric study. *Brain Research Bull*. 1993; 31 (5): 565–572. DOI: 10.1016/0361-9230 (93)90124-t.
19. *Yao F.S.F., Tseng C.C.A., Ho C.Y.A., Levin S.K., Illner P.* Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth*. 2004; 18 (5): 552–558. DOI: 10.1053/j.jvca. 2004.07.007. PMID: 15578464.
20. *Panch S.R., Montemayor-Garcia C., Klein H.G.* Hemolytic transfusion reactions. *N Engl J Med*. 2019; 381 (2): 150–162. DOI: 10.1056/NEJMra1802338. PMID: 31291517.
21. *Ferraris V.A., Ballert E.Q., Mahan A.* The relationship between intraoperative blood transfusion and postoperative systemic inflammatory response syndrome. *Am J Surg*. 2013; 205 (4): 457-465. DOI: 10.1016/j.amjsurg.2012.07.042. PMID: 23414633.
22. *Ивкин А.А., Борисенко Д.В., Цепокина А.В., Григорьев Е.В., Шукевич Д.Л.* Отказ от эритроцитарной массы для заполнения аппарата искусственного кровообращения как основа периоперационной профилактики церебрального повреж-

дения у детей при кардиохирургических операциях. *Анестезиология и реаниматология*. 2021; 4: 54–61. DOI: 10.17116/anaesthesiology202104154. [*Ivkin A.A., Borisenko D.V., Tsepokina A.V., Grigoriev E.V., Shukevich D.L.* Renouncement of red blood cell for heart-lung machine filling as the basis for perioperative prevention of cerebral injury in children undergoing cardiac surgery. *Anesthesiology and intensive care/Anesteziologiya i reanimatologiya*. (In Russ.). 2021; 4: 54–61. DOI: 10.17116/anaesthesiology202104154].

23. *Boehne M., Sasse M., Karch A., Dziuba F., Horke A., Kaussen T., Mikolajczyk R., Beerbaum P., Jack T.* Systemic inflammatory response syndrome after pediatric congenital heart surgery: Incidence, risk factors, and clinical outcome. *J Card Surg*. 2017; 32 (2): 116-125. DOI: 10.1111/ jocs.12879. PMID: 27928843.
24. *Mulder H.D., Augustijn Q.J., van Woensel J.B., Bos A.P., Juffermans N,P,, Wösten-van Asperen R.M.* Incidence, risk factors, and outcome of transfusion-related acute lung injury in critically ill children: a retrospective study. *J Crit Care*. 2015; 30 (1): 55–59. DOI: 10.1016/ j.jcrc.2014.10.005. PMID: 25457117.
25. *Atwa Z.T., Abdel Wahed W.Y.* Transfusion transmitted infections in frequently transfused thalassemic children living in Fayoum Governorate, Egypt: Current prevalence and risk factors. *J Infect Public Health*. 2017; 10 (6): 870–874. DOI: 10.1016/j.jiph.2017.02.012. PMID: 28292647.
26. *Ивкин А.А., Григорьев Е.В., Цепокина А.В., Шукевич Д.Л.* Послеоперационный делирий у детей при коррекции врожденных септальных пороков сердца. *Вестник анестезиологии и реаниматологии*. 2021; 18 (2): 62–68. DOI: 10.21292/2078-5658-2021-18-2-62-68 [*Ivkin A.A., Grigoriev E.V., Tsepokina A.V., Shukevich D.L.* Postoperative delirium in children undergoing correction of congenital septal heart defects. *Messenger of Anesthesiology and Resuscitation/Vestnik anesthesiologii i reanimatologii*. (in Russ.). 2021; 18 (2): 62–68. DOI: 10.21292/2078-5658-2021-18-2-62-68].
27. *Naguib A.N., Winch P.D., Tobias J.D., Simsic J., Hersey D., Nicol K., Preston T., Gomez D., McConnell P., Galantowicz M.* A single-center strategy to minimize blood transfusion in neonates and children undergoing cardiac surgery. *Paediatr Anaesth*. 2015; 25 (5): 477–86. DOI: 10.1111/pan.12604. PMID: 25581204.
28. *Ивкин А.А., Корнелюк Р.А., Борисенко Д.В., Нохрин А.В., Шукевич Д.Л.* Искусственное кровообращение без использования компонентов донорской крови при операции на сердце у ребенка весом 8 кг: клинический случай. *Патология кровообращения и кардиохирургия*. 2018; 20 (2): 62–67. DOI: 10.21688/1681-3472-2018-2-63-67. [*Ivkin A.A., Kornelyuk R.A., Borisenko D.V., Nokhrin A.V., Shukevich D.L.* Cardiopulmonary bypass without the use of donor blood components during heart surgery in a child weighing 8 kg: a clinical case. *Pathology of blood circulation and cardiac surgery /Patologiya krovoobrashcheniya i kardiohirurgiya*. (in Russ.). 2018; 22 (2): 62–67. DOI: 10.21688/1681-3472-2018-2-63-67].

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